REMARKS

The Office Action of July 8, 2003 presents the examination of claims 1-18. Claim 1 is amended to recite, "wherein 1 g of the lipophilic drug requires 1000 ml or more of water to be dissolved." Support for this phrase is found in the specification, such as on page 11, lines 11-19. Thus, no new matter is inserted into the application.

Interview

A personal interview was held with the Examiner at the United States Patent and Trademark Office on October 22, 2003. The Examiner's assistance in advancing prosecution of the present application is greatly appreciated.

Rejection under 35 U.S.C. § 103(a)

Fujioka '547 in view of Sankyo Co. Ltd.

The Examiner rejects claims 1-5, 8-12, and 15-18 under 35 U.S.C. § 103(a) for allegedly being obvious over Fujioka '547 (U.S. Patent 5,851,547) in view of Sankyo Co. Ltd. (JP 57093909 A). Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

First, Applicants respectfully submit that the lipophilic drugs disclosed by Sankyo Co. Ltd. are not encompassed by the instant claims. In particular, claim 1 (as amended) recites,

> A sustained release preparation of a lipophilic drug, comprising a drug dispersion wherein the lipophilic drug and a water-soluble substance are dispersed, as a solid particle at the body temperature of an animal or a human being to which the preparation is to be administered, in a water-impermeable and biocompatible material,
>
> wherein 1 g of the lipophilic drug requires 1000 ml or more of water to be dissolved.

As discussed during the interview on October 22, 2003, the lipophilic drugs of the present invention are very hard to dissolve (i.e., 1 g of the lipophilic drug requires 1000 ml or more of water to be dissolved). See, page 11, lines 11-19 of the specification. On the other hand, the lipophilic drugs disclosed in Sankyo Co. Ltd., i.e., daunorubicin and mitomycin, are either slightly soluble in water or freely soluble in water, respectively.

As shown in the U.S. Pharmacopoeia (1995), daunorubicin is characterized as "freely soluble in water," meaning that from 1 to 10 parts of solvent is required for 1 part of solute, and mitomycin is characterized as "slightly soluble in water," meaning that from 100 to 1000 parts of solvent is required for 1 part of solute. See, pages 2071, 2082, and 2097 of the U.S. Pharmacopoeia (attached hereto as **Exhibit 1**).

Applicants respectfully submit that the limitation on lipophilicity in claim 1 excludes the drugs taught by Sankyo Co. Ltd. and disposes of the Sankyo Co. Ltd. reference, since the lipophilic drugs encompassed by claim 1 require 1000 ml or more of water to be dissolved, whereas the lipophilic drugs

encompassed by the Sankyo Co. Ltd. reference require less than 1000 ml to be dissolved. Further, it is believed that the Examiner agreed during the Interview that the drugs taught by Sankyo Co. Ltd. are excluded from a lipophilic drug which requires 1000 or more parts solvent to one part solute.

As a side matter, the Examiner inquired during the Interview whether the definitions for lipophilicity provided in the specification (which references the Pharmacopoeia of Japan) are the same as for the U.S. Pharmacopoeia. Applicants respectfully confirm that the definitions for lipophilicity provided in the specification are consistent throughout the art as found in the Japanese Pharmacopoeia (1996) and the European Pharmacopoeia (1997), attached hereto as **Exhibit 2** (including translation) and **Exhibit 3**, respectively.

Second, Applicants respectfully submit that there is no motivation to combine Fujioka '547 and Sankyo Co. Ltd. On page 4 of the Office Action, the Examiner states, "[I]t would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the composition of Fujioka '547 by using lipophilic drugs taught by Sankyo Co. Ltd…." Applicants respectfully disagree; contrary to the Examiner's assertions, the skilled artisan would in no way be motivated to combine Fujioka '547 and Sankyo Co. Ltd.

Sankyo Co. Ltd. is directed to liposome formulations. On page 2 (left-hand upper column, line 17 to the right-hand upper

column, line 18), Sankyo Co. Ltd. discloses the following:

- There was a need in the art for a pharmaceutical preparation having directivity toward specific internal organs in view of various advantages, such as increased pharmacological activity, reduced dosage, and decreased side-effects;
- The inventors succeeded in producing a liposome formulation, wherein a fat-soluble carcinostatic agent is encapsulated at a high concentration, although it has been unsuccessful in encapsulation at a low concentration; and
- It was found that the obtained formulation showed directivity towards specific internal organs when it was administered to a living body.

Thus, Sankyo Co. Ltd. teaches the specific effects (i.e., decreased side-effects) derived from the high concentration of the carcinostatic agent encapsulated into a liposome. However, the preparation of Fujioka '547 is not a liposome formulation. Therefore, there would be no motivation for one skilled in the art to "pick and choose" a lipophilic drug from the Sankyo Co. Ltd. formulation for use in the Fujioka '547 formulation. Specifically, the skilled artisan would not consider the specific disclosure of highly concentrated carcinostatic agent in a liposome formulation as taught in Sankyo Co. Ltd. to be applicable to the Fujioka '547 formulation. Instead, the skilled

artisan would rely on Sankyo Co. Ltd. merely to teach the specific liposome formulation (i.e., a fat-soluble carcinostatic agent encapsulated at a high concentration) for administration to specific internal organs.

In summary, the present invention is not obvious over Fujioka '547 in view of Sankyo Co. Ltd. First, the instant claims exclude drugs disclosed in Sankyo Co. Ltd. Second, the skilled artisan would not be motivated to combine Fujioka '547 and Sankyo Co. Ltd. For these reasons, withdrawal of the instant rejection is respectfully requested.

Fujioka '547 in view of Sankyo Co. Ltd. and Fujioka '253

The Examiner rejects claims 1-6, 8-13, and 15-18 under 35 U.S.C. § 103(a) for allegedly being obvious over Fujioka '547 (U.S. Patent 5,851,547) in view of Fujioka '253 (U.S. Patent 4,985,253) and further in view of Sankyo Co. Ltd. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

As discussed during the Interview, the present invention utilizes the water-soluble substance (such as PEG) in a solid form, rather than a liquid form, as taught by Fujioka '253. The use of a solid form surprisingly shows enhancement of drug release, and the skilled artisan (given the knowledge known in the art at the time) would not expect that enhancement.

As described in the instant specification, it was known in

the art that drug release mechanisms for lipophilic drugs from a matrix-type preparation involved diffusion of the drug into the matrix. See, "PROBLEM TO BE SOLVED BY THE INVENTION," pages 4-5 of the specification. However, there was a problem in that the release of the drug in a sufficiently effective amount for a prolonged period could not be accomplished. To solve this problem, the Examiner asserts that it would have been obvious for one of ordinary skill in the art to modify the composition of Fujioka '547 by using polyethylene glycol disclosed in Fujioka '253 in order to control the release rate of the pharmaceutical substance. Applicants respectfully disagree for the following reasons.

First, Fujioka '253 specifically teaches PEG400 and PEG200 as polyethylene glycol, which are a liquid at room temperature. On the other hand, the water-soluble substance of the present invention is a "solid particle," as recited in claim 1. Therefore, polyethylene glycol disclosed in Fujioka '253 is not equivalent to the water-soluble substance of the present invention.

Second, prior to the present invention, one of ordinary skill in the art would believe that the use of polyethylene glycol in a solid state would not enhance the diffusion rate of a drug, and would, in fact, lead to a decrease in the release rate of the drug. As described in page 3, lines 24-28 of the specification, it has been reported that a preparation containing

a liquid additive showed enhancement of lipophilic drug permeation while a preparation containing a solid additive showed a decrease in lipophilic drug permeation. See, *Proceed. Intern. Symp. Control. Rel. Bioact. Mater.*, 12, 145-146 (1985) attached hereto as **Exhibit 4**.

For example, Table 1 of the article (page 146) shows that a liquid additive leads to enhancement of progesterone permeation (PER) up to 4.9, whereas a solid additive (a water-soluble substance such as lactose, sodium lauryl sulfate, etc.) leads to a decrease in progesterone permeation (less than 1.3 of PER), compared with Control (1.9 of PER). As such, the state of the art taught away from the use of a solid additive in a drug formulation. In view of this teaching, the skilled artisan would not be motivated to use polyethylene glycol in a solid state, even if he might use a liquid polyethylene glycol to control release rate of the drug.

Contrary to the above expectation of those skilled in the art, the present invention surprisingly shows enhancement of drug release by using polyethylene glycol in a solid state as a water-soluble substance. Fig. 3 of the present application shows drug-release behavior of the preparation as defined in claim 2 (Preparation 1) and the preparation wherein the drug dispersion does not contain a water-soluble substance (Reference preparation).

	Preparation 1	**Reference Preparation**
Drug dispersion	ivermectin + polyethylene glycol/silicone	ivermectin/silicone
Coating layer	silicone	silicone

As shown in Fig. 3, Preparation 1 showed an enhanced release rate, which is several times greater than that of the Reference Preparation containing no water-soluble substance. Additionally, Preparation 1 showed an almost zero-order release behavior. As explained in the specification, this effect is derived from the unique release mechanism of the preparation by use of the construction defined in the claims. See, page 7, line 14 to page 8, line 4 of the specification, wherein it is explained:

(a) Consecutive dissolution in water of a water-soluble substance dispersed in the drug dispersion allows infiltration of water from the surface to the inside of the drug dispersion,. thereby contact of a lipophilic drug with water is enhanced to increase the release of the lipophilic drug. Thus, the preparation of the invention can enhance the release of a lipophilic drug, which is hard to solubilize in water; and

(b) By selecting a water-soluble substance, the release rate of a lipophilic drug can be varied. The release of a lipophilic drug can be enhanced by using, for example, an amphipathic substance as a water-soluble

substance. That is, the release of the lipophilic drug can be further enhanced by such amphipathic substance, which has been dissolved in water infiltrated into the drug dispersion in a similar manner as described in (a).

Thus, the drug release mechanism of the present invention is not a mechanism known in the art wherein dispersion of a drug in a matrix is principally involved, and therefore, the effect derived from this mechanism would not have been obvious to those skilled in the art at the time the present invention was made.

During the Interview, the Examiner questioned whether claim 1, as currently drafted, requires that the water-soluble substance be in solid form. For instance, the Examiner stated that it is known in the art that some compositions are in liquid form until they contact water, at which point they form a solid. In response, Applicants do not know of any pharmaceutical additives of this kind which have such unusual properties. If necessary, the Examiner is respectfully requested to clarify her remarks.

In any event, those skilled in the art who have read the description understand that the present invention encompasses a pharmaceutical formulation implantable in a living body. See, for example, page 1, lines 11-13, and page 2, lines 9-13 of the specification. In view of the teachings in the specification, the skilled artisan would utilize a water soluble substance as

taught in the specification for this type of formulation, and therefore, would not have an idea to use substances having such unusual properties for the formulation. Indeed, the water-soluble substances specifically provided in the specification (e.g., page 12, lines 8-19) are all those that are in a solid state until they contact water, at which point they are gradually resolved in water. Accordingly, it is apparent to those skilled in the art upon reading the description that the water-soluble substance in claim 1 is not of the kind as stated by the Examiner.

The solid form of the water-soluble substance before contact with water is apparent from the language in claim 1, namely "a water-soluble substance are (is) dispersed, as a solid particle." However, the Examiner states that some compositions are in liquid form until they contact water, and as such, claim 1 could encompass water-soluble substances may be in liquid form before contact with water. Applicants respectfully disagree that claim 1 could encompass such a substance; the definition of "water-soluble substance" *per se* means the substance is in a solid state prior to contact with water. Specifically, a "water-soluble substance" is in a solid state before contact with water, but is gradually resolved in water after contact with water, contrary to the Examiner's presupposition that the water-soluble substance is in solid form both before and after contact with water.

In summary, the water-soluble substance recited in claim 1

is in solid state before contact with water, but is gradually resolved in water after contact with water. Unlike the present invention, Fujioka '253 teaches PEG in a liquid state prior to contact with water. Further, the skilled artisan would not be motivated to modify PEG from a liquid state to a solid state, since the state of the art taught that the use of a liquid additive enhanced drug release, whereas the use of a solid additive decreased drug release.

For all of these reasons, the present invention is not obvious Fujioka '547 in view of Fujioka '253 and further in view of Sankyo Co. Ltd. Withdrawal of the instant rejection is therefore respectfully requested.

Fujioka '547 in view of Sankyo Co. Ltd. and Remington's Pharmaceutical Sciences

The Examiner rejects claims 1-5, 7-12, and 14-18 under 35 U.S.C. § 103(a) for allegedly being obvious over Fujioka '547 in view of Sankyo Co. Ltd. and further in view of Remington's Pharmaceutical Sciences. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

The Examiner relies on Remington's Pharmaceutical Sciences to teach sodium lauryl sulfate. The Examiner states that one of ordinary skill in the art would expect to achieve the desired constant release rate of a drug using sodium lauryl sulfate in

the inner layer composed of silicone elastomer. See, page 7, lines 16 and 17 of the Office Action. Applicants respectfully disagree because sodium lauryl sulfate is a solid, and therefore, the skilled artisan would not expect the use of sodium lauryl sulfate to lead to an increase in the release rate of a drug. Instead, the skilled artisan would believe that the use of sodium lauryl sulfate would result in a decrease in drug release, for the same reasons that the skilled artisan would believe that the use of PEG in a solid state would result in a decrease in drug release, as discussed above.

In contrast, the preparation of the present invention using a water-soluble substance, such as PEG or sodium lauryl sulfate, in a solid state shows drug release behavior that would not be obvious to those skilled in the art. The drug release behavior of the present invention resulting from the unique release mechanism is surprising, and therefore, the present invention as claimed is not obvious to those skilled in the art. Withdrawal of the instant rejection is therefore respectfully requested.

Summary

Applicants respectfully submit that the above amendments and/or remarks fully address and overcome the rejections of record. The instant claims are now in condition for allowance. Early and favorable action by the Examiner is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. 45,702) at the telephone number of the undersigned below.

Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), the Applicants hereby petition for an extension of one (1) month to November 8, 2003, in which to file a reply to the Office Action. The required fee of $110.00 is enclosed herewith.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachments:

Exhibit 1: The United States Pharmacopeia 23, 1995, pages 2071, 2082, 2097;

Exhibit 2: English translation of the relevant parts in "Japanese Pharmacopoeia", and Japanese Pharmacopoeia, 1996, pages A-51-A-52;

Exhibit 3: European Pharmacopoeia, Third Edition, 1997, page 3;

Exhibit 4: W. Pfister et al., Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 12, (1985), pages 145-146.

1995

USP 23

NF 18

THE UNITED STATES PHARMACOPEIA

THE NATIONAL FORMULARY

By authority of the United States Pharmacopeial Convention, Inc., meeting at Washington, D.C., March 8–10, 1990. Prepared by the Committee of Revision and published by the Board of Trustees

Official from January 1, 1995

USP SINCE 1820

UNITED STATES PHARMACOPEIAL CONVENTION, INC.
12601 Twinbrook Parkway, Rockville, MD 20852

DESCRIPTION AND SOLUBILITY

Description and Relative Solubility of USP and NF Articles

The "description" and "solubility" statements pertaining to an article (formerly included in the individual monograph) are general in nature. The information is provided for those who use, prepare, and dispense drugs, solely to indicate descriptive and solubility properties of an article complying with monograph standards. The properties are not in themselves standards or tests for purity even though they may indirectly assist in the preliminary evaluation of the integrity of an article.

Taste and Odor

Organoleptic characteristics are indicated in many instances because they may be useful and descriptive properties of substances. However, they are not meant to be applied as tests for identifying materials.

The inclusion of odor or taste among other descriptive properties may aid in identifying the causative agent following accidental exposure to or contact with a substance. This information is provided as a warning or to make an individual aware of sensations that may be encountered. The use of odor or taste as a test for identification or content is strongly discouraged.

The characteristic odor of a volatile substance becomes apparent immediately on opening a container of it. The odor may be agreeable (e.g., Peppermint Oil), unpleasant (e.g., Sulfur Dioxide), or potentially hazardous on prolonged exposure (e.g., Coal Tar). Moreover, an unexpected odor may be encountered if the characteristics of a substance are not know or if a container is incorrectly labeled. Consequently, containers of such substances should be opened cautiously, preferably in a well-ventilated fume hood. A characteristic taste or sensation produced in the oral cavity likewise is apparent if traces of residue materials on fingers are inadvertently brought into contact with the tongue or adjacent mucosal tissues.

Solubility

Only where a special, quantitative solubility test is given in the individual monograph, and is designated by a test heading, is it a test for purity.

The approximate solubilities of Pharmacopeial and National Formulary substances are indicated by the descriptive terms in the accompanying table. The term "miscible" as used in this Pharmacopeia pertains to a substance that yields a homogeneous mixture when mixed in any proportion with the designated solvent.

Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble, or Insoluble	10,000 and over

Soluble Pharmacopeial and National Formulary articles, when brought into solution, may show traces of physical impurities, such as minute fragments of filter paper, fibers, and other particulate matter, unless limited or excluded by definite tests or other specifications in the individual monographs.

Acacia: Is practically odorless and produces a mucilaginous sensation on the tongue. Insoluble in alcohol. Optical rotation varies depending on the source of Acacia. For example, specific rotation values, calculated on the anhydrous basis and determined on a 1.0% (w/v) solution, usually are between −25° and −35° for *Acacia senegal* and between +35° and +60° for *Acacia seyal*. *NF category:* Emulsifying and/or solubilizing agent; suspending and/or viscosity-increasing agent; tablet binder.

Acetaminophen: White, odorless, crystalline powder, having a slightly bitter taste. Soluble in boiling water and in 1 *N* sodium hydroxide; freely soluble in alcohol.

Acetazolamide: White to faintly yellowish white, crystalline, odorless powder. Very slightly soluble in water; sparingly soluble in practically boiling water; slightly soluble in alcohol.

Sterile Acetazolamide Sodium: White solid, having the characteristic appearance of freeze-dried products.

Acetic Acid: Clear, colorless liquid, having a strong, characteristic odor, and a sharply acid taste. Specific gravity is about 1.045. Miscible with water, with alcohol, and with glycerin. *NF category:* Acidifying agent; buffering agent.

Glacial Acetic Acid: Clear, colorless liquid, having a pungent, characteristic odor and, when well diluted with water, an acid taste. Boils at about 118°. Specific gravity is about 1.05. Miscible with water, with alcohol, and with glycerin. *NF category:* Acidifying agent.

Acetohexamide: White, crystalline, practically odorless powder. Practically insoluble in water and in ether; soluble in pyridine and in dilute solutions of alkali hydroxides; slightly soluble in alcohol and in chloroform.

Acetohydroxamic Acid: White, slightly hygroscopic, crystalline powder. Melts, after drying at about 80° for 2 to 4 hours, at about 88°. Freely soluble in water and in alcohol; very slightly soluble in chloroform.

Acetone: Transparent, colorless, mobile, volatile liquid, having a characteristic odor. A solution (1 in 2) is neutral to litmus. Miscible with water, with alcohol, with ether, with chloroform, and with most volatile oils. *NF category:* Solvent.

Acetylcholine Chloride: White or off-white crystals or crystalline powder. Very soluble in water; freely soluble in alcohol; insoluble in ether. Is decomposed by hot water and by alkalies.

Acetylcysteine: White, crystalline powder, having a slight acetic odor. Freely soluble in water and in alcohol; practically insoluble in chloroform and in ether.

Acyclovir: White to off-white crystalline powder. Melts at temperatures higher than 250°, with decomposition. Soluble in 0.1 *N* hydrochloric acid; sparingly soluble in water; insoluble in alcohol.

Adenine: White crystals or crystalline powder. Is odorless and tasteless. Very slightly soluble in water; sparingly soluble in boiling water; slightly soluble in alcohol; practically insoluble in ether and in chloroform.

Agar: Odorless or has a slight odor, and produces a mucilaginous sensation on the tongue. Insoluble in cold water; soluble in boiling water. *NF category:* Suspending and/or viscosity-increasing agent.

some decomposition (see *Melting Range or Temperature* ⟨741⟩). Insoluble in water; freely soluble in chloroform; soluble in dioxane; sparingly soluble in acetone; slightly soluble in alcohol.

Purified Cotton: White, soft, fine filament-like hairs appearing under the microscope as hollow, flattened, and twisted bands, striate and slightly thickened at the edges. Is practically odorless and practically tasteless. Insoluble in ordinary solvents; soluble in ammoniated cupric oxide TS.

Cottonseed Oil: Pale yellow, oily liquid. Is odorless or nearly so, and has a bland taste. At temperatures below 10° particles of solid fat may separate from the Oil, and at about 0° to −5° the Oil becomes a solid or nearly so. Slightly soluble in alcohol. Miscible with ether, with chloroform, with solvent hexane, and with carbon disulfide. *NF category:* Solvent; vehicle (oleaginous).

Creatinine: White crystals or crystalline powder; odorless. Soluble in water; slightly soluble in alcohol; practically insoluble in acetone, in ether, and in chloroform. *NF category:* Bulking agent for freeze-drying.

Cresol: Colorless, or yellowish to brownish yellow, or pinkish, highly refractive liquid, becoming darker with age and on exposure to light. Has a phenol-like, sometimes empyreumatic odor. A saturated solution of it is neutral or only slightly acid to litmus. Sparingly soluble in water, usually forming a cloudy solution; dissolves in solutions of fixed alkali hydroxides. Miscible with alcohol, with ether, and with glycerin. *NF category:* Antimicrobial preservative.

Cromolyn Sodium: White, odorless, crystalline powder. Is tasteless at first, with a slightly bitter aftertaste. Is hygroscopic. Soluble in water; insoluble in alcohol and in chloroform.

Cromolyn Sodium for Inhalation: White to creamy white, odorless, hygroscopic, and very finely divided powder.

Croscarmellose Sodium: White, free-flowing powder. Partially soluble in water; insoluble in alcohol, in ether, and in other organic solvents. *NF category:* Tablet disintegrant.

Crospovidone: White to creamy-white, hygroscopic powder, having a faint odor. Insoluble in water and in ordinary organic solvents. *NF category:* Tablet disintegrant.

Crotamiton: Colorless to slightly yellowish oil, having a faint amine-like odor. Soluble in alcohol and in methanol.

Cupric Chloride: Bluish green, deliquescent crystals. Freely soluble in water; soluble in alcohol; slightly soluble in ether.

Cupric Sulfate: Deep blue, triclinic crystals or blue, crystalline granules or powder. It effloresces slowly in dry air. Its solutions are acid to litmus. Freely soluble in water and in glycerin; very soluble in boiling water; slightly soluble in alcohol.

Cyanocobalamin: Dark red crystals or amorphous or crystalline red powder. In the anhydrous form, it is very hygroscopic and when exposed to air it may absorb about 12% of water. Sparingly soluble in water; soluble in alcohol; insoluble in acetone, in chloroform, and in ether.

Cyclizine: White, or creamy white, crystalline, practically odorless powder. Slightly soluble in water; soluble in alcohol and in chloroform.

Cyclizine Hydrochloride: White, crystalline powder or small, colorless crystals. Is odorless or nearly so, and has a bitter taste. Melts indistinctly at about 285°, with decomposition. Slightly soluble in water and in alcohol; sparingly soluble in chloroform; insoluble in ether.

Cyclobenzaprine Hydrochloride: White to off-white, odorless, crystalline powder. Freely soluble in water, in alcohol, and in methanol; sparingly soluble in isopropanol; slightly soluble in chloroform and in methylene chloride; insoluble in hydrocarbons.

Cyclopentolate Hydrochloride: White, crystalline powder, which upon standing develops a characteristic odor. Its solutions are acid to litmus. Melts at about 138°, the melt appearing opaque. Very soluble in water; freely soluble in alcohol; insoluble in ether.

Cyclophosphamide: White, crystalline powder. Liquefies upon loss of its water of crystallization. Soluble in water and in alcohol.

Cyclopropane: Colorless gas having a characteristic odor. Has a pungent taste. One liter at a pressure of 760 mm and a temperature of 0° weighs about 1.88 g. One volume dissolves in about 2.7 volumes of water at 15°. Freely soluble in alcohol; soluble in fixed oils.

Cycloserine: White to pale yellow, crystalline powder. Is odorless or has a faint odor. Is hygroscopic and deteriorates upon absorbing water. Its solutions are dextrorotatory. Freely soluble in water.

Cyproheptadine Hydrochloride: White to slightly yellow, odorless or practically odorless, crystalline powder. Slightly soluble in water; freely soluble in methanol; soluble in chloroform; sparingly soluble in alcohol; practically insoluble in ether.

Cysteine Hydrochloride: White crystals or crystalline powder. Soluble in water, in alcohol, and in acetone.

Cytarabine: Odorless, white to off-white, crystalline powder. Freely soluble in water; slightly soluble in alcohol and in chloroform.

Dactinomycin: Bright red, crystalline powder. Is somewhat hygroscopic and is affected by light and by heat. Soluble in water at 10° and slightly soluble in water at 37°; freely soluble in alcohol; very slightly soluble in ether.

Danazol: White to pale yellow, crystalline powder. Melts at about 225°, with some decomposition. Practically insoluble or insoluble in water and in hexane; freely soluble in chloroform; soluble in acetone; sparingly soluble in alcohol and in benzene; slightly soluble in ether.

Dapsone: White or creamy white, crystalline powder. Is odorless and has a slightly bitter taste. Very slightly soluble in water; freely soluble in alcohol; soluble in acetone and in dilute mineral acids.

Daunorubicin Hydrochloride: Orange-red, crystalline, hygroscopic powder. Freely soluble in water and in methanol; slightly soluble in alcohol; very slightly soluble in chloroform; practically insoluble in acetone.

Deferoxamine Mesylate: White to off-white powder. Freely soluble in water; slightly soluble in methanol.

Dehydrocholic Acid: White, fluffy, odorless powder, having a bitter taste. Practically insoluble in water; soluble in glacial acetic acid and in solutions of alkali hydroxides and carbonates; slightly soluble in alcohol and in ether; sparingly soluble in chloroform (the solutions in alcohol and in chloroform usually are slightly turbid).

Demecarium Bromide: White or slightly yellow, slightly hygroscopic, crystalline powder. Freely soluble in water and in alcohol; soluble in ether; sparingly soluble in acetone.

Demeclocycline: Yellow, crystalline, odorless powder, having a bitter taste. Sparingly soluble in water; soluble in alcohol. Dissolves readily in 3 *N* hydrochloric acid and in alkaline solutions.

Demeclocycline Hydrochloride: Yellow, crystalline, odorless powder, having a bitter taste. Sparingly soluble in water and in solutions of alkali hydroxides and carbonates; slightly soluble in alcohol; practically insoluble in acetone and in chloroform.

Denatonium Benzoate: Freely soluble in water and in alcohol; very soluble in chloroform and in methanol; very slightly soluble in ether. *NF category:* Alcohol denaturant.

Desipramine Hydrochloride: White to off-white, crystalline powder. Melts at about 213°. Soluble in water and in alcohol; freely soluble in methanol and in chloroform; insoluble in ether.

Desoximetasone: White to practically white, odorless, crystalline powder. Insoluble in water; freely soluble in alcohol, in acetone, and in chloroform.

Mexiletine Hydrochloride: White powder. Freely soluble in dehydrated alcohol and in water; slightly soluble in acetonitrile; practically insoluble in ether. Optically inactive (1 in 20 solution in water).

Sterile Mezlocillin Sodium: White to pale yellow, crystalline powder. Freely soluble in water.

Miconazole: White to pale cream powder. Melts in the range of 78° to 82°. Insoluble in water; soluble in ether; freely soluble in alcohol, in methanol, in isopropyl alcohol, in acetone, in propylene glycol, in chloroform, and in dimethylformamide.

Miconazole Nitrate: White or practically white, crystalline powder, having not more than a slight odor. Melts in the range of 178° to 183°, with decomposition. Insoluble in ether; very slightly soluble in water and in isopropyl alcohol; slightly soluble in alcohol, in chloroform, and in propylene glycol; sparingly soluble in methanol; soluble in dimethylformamide; freely soluble in dimethyl sulfoxide.

Mineral Oil: Colorless, transparent, oily liquid, free or practically free from fluorescence. Is odorless and tasteless when cold, and develops not more than a faint odor of petroleum when heated. Insoluble in water and in alcohol; soluble in volatile oils. Miscible with most fixed oils but not with castor oil. *NF category:* Solvent; vehicle (oleaginous).

Light Mineral Oil: Colorless, transparent, oily liquid, free, or practically free, from fluorescence. Is odorless and tasteless when cold, and develops not more than a faint odor of petroleum when heated. Insoluble in water and in alcohol; soluble in volatile oils. Miscible with most fixed oils, but not with castor oil. *NF category:* Tablet and/or capsule lubricant; vehicle (oleaginous).

Minocycline Hydrochloride: Yellow, crystalline powder. Soluble in water and in solutions of alkali hydroxides and carbonates; slightly soluble in alcohol; practically insoluble in chloroform and in ether.

Minoxidil: White to off-white, crystalline powder. Melts in the approximate range of between 248° and 268°, with decomposition. Soluble in alcohol and in propylene glycol; sparingly soluble in methanol; slightly soluble in water; practically insoluble in chloroform, in acetone, in ethyl acetate, and in hexane.

Mitomycin: Blue-violet, crystalline powder. Slightly soluble in water; soluble in acetone, in methanol, in butyl acetate, and in cyclohexanone.

Mitotane: White, crystalline powder, having a slight, aromatic odor. Practically insoluble in water; soluble in alcohol, in ether, in solvent hexane, and in fixed oils and fats.

Mitoxantrone Hydrochloride: Dark blue powder. Sparingly soluble in water; slightly soluble in methanol; practically insoluble in acetone, in acetonitrile, and in chloroform.

Monobenzone: White, odorless, crystalline powder. Practically insoluble in water; soluble in alcohol, in chloroform, in ether, and in acetone.

Monobenzone Ointment: Dispersible with, but not soluble in, water.

Mono- and Di-glycerides: Varies in consistency from yellow liquids through ivory-colored plastics to hard, ivory-colored solids having a bland odor and taste. Insoluble in water; soluble in alcohol, in ethyl acetate, in chloroform, and in other chlorinated hydrocarbons.

Monoethanolamine: Clear, colorless, moderately viscous liquid, having a distinctly ammoniacal odor. Miscible with water, with acetone, with alcohol, with glycerin, and with chloroform. Immiscible with ether, with solvent hexane, and with fixed oils, although it dissolves many essential oils.

Mono- and Di-acetylated Monoglycerides: White to pale yellow, waxy solid, melting at about 45°. Soluble in ether and in chloroform; slightly soluble in carbon disulfide; insoluble in water. *NF category:* Plasticizer.

Monosodium Glutamate: White, practically odorless, free-flowing crystals or crystalline powder. Freely soluble in water; sparingly soluble in alcohol. May have either a slightly sweet or a slightly salty taste. *NF category:* Flavors and perfumes.

Monothioglycerol: Colorless or pale yellow, viscous liquid, having a slight sulfidic odor. Is hygroscopic. Miscible with alcohol. Freely soluble in water; insoluble in ether. *NF category:* Antioxidant.

Morphine Sulfate: White, feathery, silky crystals, cubical masses of crystals, or white, crystalline powder. Is odorless, and when exposed to air it gradually loses water of hydration. Darkens on prolonged exposure to light. Soluble in water; freely soluble in hot water; slightly soluble in alcohol but more so in hot alcohol; insoluble in chloroform and in ether.

Mumps Skin Test Antigen: Slightly turbid liquid.

Mumps Virus Vaccine Live: Solid having the characteristic appearance of substances dried from the frozen state. The Vaccine is to be constituted with a suitable diluent just prior to use. Constituted vaccine undergoes loss of potency on exposure to sunlight.

Mupirocin: White to off-white, crystalline solid. Freely soluble in acetone, in chloroform, in dehydrated alcohol, and in methanol; slightly soluble in ether; very slightly soluble in water.

Myristyl Alcohol: White wax-like mass. Soluble in ether; slightly soluble in alcohol; insoluble in water.

Nadolol: White to off-white, practically odorless, crystalline powder. Freely soluble in alcohol and in methanol; slightly soluble in chloroform, in methylene chloride, in isopropyl alcohol, and in water; insoluble in acetone, in benzene, in ether, in hexane, and in trichloroethane.

Nafcillin Sodium: White to yellowish white powder, having not more than a slight characteristic odor. Freely soluble in water and in chloroform; soluble in alcohol.

Nafcillin Sodium for Injection: White to yellowish white powder, having not more than a slight characteristic odor. Freely soluble in water and in chloroform; soluble in alcohol.

Nalidixic Acid: White to very pale yellow, odorless, crystalline powder. Soluble in chloroform, in methylene chloride, and in solutions of fixed alkali hydroxides and carbonates; slightly soluble in acetone, in alcohol, in methanol, and in toluene; very slightly soluble in ether and in water.

Naloxone Hydrochloride: White to slightly off-white powder. Its aqueous solution is acidic. Soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in ether and in chloroform.

Naloxone Hydrochloride Injection: Clear, colorless liquid.

Nandrolone Decanoate: Fine, white to creamy white, crystalline powder. Is odorless, or may have a slight odor. Practically insoluble in water; soluble in chloroform, in alcohol, in acetone, and in vegetable oils.

Naphazoline Hydrochloride: White, crystalline powder. Is odorless and has a bitter taste. Melts at a temperature of about 255°, with decomposition. Freely soluble in water and in alcohol; very slightly soluble in chloroform; practically insoluble in ether.

Naproxen: White to off-white, practically odorless, crystalline powder. Practically insoluble in water; freely soluble in chloroform and in dehydrated alcohol; soluble in alcohol; sparingly soluble in ether.

Naproxen Sodium: White to creamy crystalline powder. Soluble in water and in methanol; sparingly soluble in alcohol; very slightly soluble in acetone; and practically insoluble in chloroform and in toluene. Melts at about 255°, with decomposition.

Natamycin: Off-white to cream-colored powder, which may contain up to 3 moles of water. Practically insoluble in water;

English translation of the relevant parts in "Japanese Pharmacopoeia"

Table in page A-51

Descriptable term	Volume of solvent required for 1g or 1 mL of solute
Very soluble	less than 1 mL
Freely soluble	from 1 to 10 mL
Soluble	from 10 to 30 mL
Sparingly soluble	from 30 to 100 mL
Slightly soluble	from 100 to 1000 mL
Very slightly soluble	from 1000 to 10000 mL
Practically insoluble	more than 10000 mL

Sentence spanning pare A-51 and page A-52

The above descriptable term is Japanese translation of USP 23. That is, in the order of top-to-bottom, "Very soluble", "Freely soluble", "Soluble", "Sparingly soluble", "Slightly soluble", "Very slightly soluble", and "Practically insoluble" correspond to the descriptable term one by one.

第十三改正
日本薬局方解説書

通　　則
製剤総則
一般試験法

1996

東京 廣川書店 刊行

ものは無色又はほとんど無色を示すものである．色調を試験するには，別に規定するもののほか，固形の医薬品はその 1 g を白紙上又は白紙上に置いた時計皿にとり，観察する．液状の医薬品は内径 15 mm の無色の試験管に入れ，白色の背景を用い，液層を 30 mm として観察する．液状の医薬品の澄明性を試験するには，黒色又は白色の背景を用い，前記の方法を準用する．液状の医薬品の蛍光を観察するには，黒色の背景を用い，白色の背景は用いない．

注 性状の項の色は判定基準となるものであるから，その試験法を定めたものである．「白色」及び「無色」という表現のなかには「ほとんど白色」及び「ほとんど無色」を含むということである．これは 食添 と解釈が同じであり，色の判定が感覚による試験であるからである．試料の量を決めた意味は，医薬品によっては大量にとった場合と少量をとった場合とによって，その色が異なって感じる場合がしばしばあるためである．また液状の医薬品については上方から観察するのと側方から観察するのとでは色が違って感じる場合があるので，通例，上方から観察する方がよい．

22 性状の項において，無臭又はにおいがないと記載したものは，においがないか，又はほとんどにおいがないことを示すものである．においを試験するには，別に規定するもののほか，固形の医薬品 1 g 又は液状の医薬品 1 mL をビーカーにとり，行う．

注 この規定も感覚による試験で，試料の量についても各国とも異なり，個人差の大きい試験法である．USP 23 は 25 g 以下の試料はそのまま，25 g 以上では，そのうちより 25 g を約 100 mL の容器にとり 15 分間空気中にさらした後，検するとなっている．また無臭とは，ほとんどにおいがないことを含むとされている．

23 性状の項において，溶解性を示す用語は次による．溶解性は，別に規定するもののほか，医薬品を固形の場合は粉末とした後，溶媒中に入れ，20 ± 5 °C で 5 分ごとに強く 30 秒間振り混ぜるとき，30 分以内に溶ける度合をいう．

用　　語	溶質 1 g 又は 1 mL を溶かすに要する溶媒量	
極めて溶けやすい		1 mL 未満
溶けやすい	1 mL 以上	10 mL 未満
やや溶けやすい	10 mL 以上	30 mL 未満
やや溶けにくい	30 mL 以上	100 mL 未満
溶けにくい	100 mL 以上	1000 mL 未満
極めて溶けにくい	1000 mL 以上	10000 mL 未満
ほとんど溶けない		10000 mL 以上

注 性状の項の溶解性は，用語の使い分けによって示す場合がほとんどである．この場合，その用語を限定することと，用語の意味を示した規定である．用語については USP 23 の用語を邦文に訳したものと同じである．上段から順次 very soluble,

freely soluble, soluble, sparingly soluble, slightly soluble, very slightly soluble, practically insoluble がこれに対応する．このうち soluble については「やや溶けやすい」とし，「溶ける」，「ほとんど溶ける」などを一般用語として自由に使えるようにしたため，これと区別の意味でいささか感覚の異なる訳語となっている．また粉末の大きさは，薬局方原案作成要領 3.10.8.4（日本薬局方フォーラム 3, No. 3 (1994)）によれば「100 号（150 μm）ふるいを通過する細末とした後」となっている．

24 医薬品の試験において，医薬品が溶媒に溶け又は混和するとは，澄明に溶けるか又は任意の割合で澄明に混和することを示し，繊維などを認めないか又は認めても極めてわずかである．

注 主として性状の項の溶解性又は純度試験の項の溶状を試験する場合の判定の基準になる規定であって，溶けるという意味は固形の医薬品が溶媒に溶けることであり，混和するとは液体の医薬品が溶媒に混ざることを意味する．この場合に，ろ紙のくずや繊維などが製造操作過程で混ざってくることがあるが，これらの物質は溶状の判定には無関係のものであるからこれを除いたもので判定して差し支えないことを認めている．つまり繊維などの試験が主眼ではない．適否に影響のあるゴミなどは，他の試験でチェックされると考えられるし，薬事法第 56 条 のうち例えば「異物が混入し，又は附着している医薬品」に相当し販売，製造等が禁止されることになる．

澄明の意味は無色ということが特に指定されない場合には，着色していても差し支えない．また，澄明度，すなわち濁度について 食系 は塩酸と硝酸銀によって生じる塩化銀の濁りを基準として規定を設定しているが，すべての場合にこれを適用するには無理があり，局 では濁度によって判定を行うような場合は，比較液の調製法を示すようにしている．

25 確認試験は，医薬品又は医薬品中に含有されている主成分などを，その特性に基づいて確認するために必要な試験である．

注 確認試験の定義である．確認試験とは identification の訳で，同定試験，定性試験などとも訳される．局 でいう確認試験はそのものを同定する試験法で，いいかえれば，「医薬品を構成する物質又は医薬品中に含有されている主成分などについて，それぞれの特異な反応を用いて特性に応じて試験し，その医薬品の同定に役だつ試験」である．確認試験としては，通例，スペクトル分析に基づく方法及び化学反応による方法などが用いられている．

26 純度試験は，医薬品中の混在物を試験するために行うもので，医薬品各条のほかの試験項目と共に，医薬品の純度を規定する試験でもあり，通例，その混在物の種類及びその量の限度を規定する．この試験の対象となる混在物は，その医薬品を製造する過程又は保存の間に混在を予想されるもの又は有害な混在物例えば重金属，ヒ素などである．また，異物を用い又は加えることが予想される場合については，その試験を行う．

注 純度試験は薬局方試験のうち最も重要なものの一つである．純度試験とは外国

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maceutical dosage forms may, under the heading Definition/ Production, require the use of certain types of container; certain other monographs may, under the heading Storage, indicate the type of container that is recommended for use.

1.4. MONOGRAPHS

TITLES

Monograph titles are in English and French in the respective versions and there is a Latin subtitle which may be used in place of the English or French title as may any synonyms declared equivalent by the competent authority.

RELATIVE ATOMIC AND MOLECULAR MASSES

The relative atomic mass (A_r) or the relative molecular mass (M_r) is shown, as and where appropriate, at the beginning of each monograph. The relative atomic and molecular masses and the molecular and graphic formulae do not constitute analytical standards for the substances described.

DEFINITION

Statements under the heading Definition constitute an official definition of the substance, preparation or other article that is the subject of the monograph.

Limits of content. Where limits of content are prescribed, they are those determined by the method described under Assay.

Vegetable drugs. In monographs on vegetable drugs, the definition indicates whether the subject of the monograph is, for example, the whole drug or the drug in powdered form. Where a monograph applies to the drug in several states, for example both to the whole drug and the drug in powdered form, the definition states this.

PRODUCTION

Statements under the heading Production draw attention to particular aspects of the manufacturing process but are not necessarily comprehensive. They constitute instructions to manufacturers. They may relate, for example, to source materials, to the manufacturing process itself and its validation and control, to in-process testing or to testing that is to be carried out by the manufacturer on the final article either on selected batches or on each batch prior to release. These statements cannot necessarily be verified on a sample of the final article by an independent analyst. The competent authority may establish that the instructions have been followed, for example, by examination of data received from the manufacturer, by inspection of manufacture or by testing appropriate samples.

The absence of a section on Production does not imply that attention to features such as those referred to above is not required. A product described in a monograph of the Pharmacopoeia is manufactured in accordance with the principles of good manufacturing practice and in accordance with relevant international agreements and supranational and national regulations governing products for human or veterinary use.

Where in the section under the heading Production a monograph on a vaccine defines the characteristics of the vaccine strain to be used, any test methods given for confirming these characteristics are provided for information as examples of suitable methods.

CHARACTERS

The statements under the heading Characters are not to be interpreted in a strict sense and are not requirements.

Solubility. In statements of solubility in the section headed Characters, the terms used have the following significance referred to a temperature between 15 °C and 25 °C.

Descriptive term	Approximate volume of solvent in millilitres per gram of solute			
Very soluble	less than	1		
Freely soluble	from	1	to	10
Soluble	from	10	to	30
Sparingly soluble	from	30	to	100
Slightly soluble	from	100	to	1000
Very slightly soluble	from	1000	to	10 000
Practically insoluble	more than			10 000

The term "partly soluble" is used to describe a mixture where only some of the components dissolve. The term "miscible" is used to describe a liquid that is miscible in all proportions with the stated solvent.

IDENTIFICATION

The tests given in the identification section are not designed to give a full confirmation of the chemical structure or composition of the product; they are intended to give confirmation, with an acceptable degree of assurance, that the article conforms to the description on the label.

Certain monographs have subdivisions entitles 'First identification' and the 'Second identification'. The test or tests that constitute the 'Second identification' may be used instead of the test or tests of the 'First identification' provided it can be demonstrated that the substance or preparation is fully traceable to a batch certified to comply with all the requirements of the monograph.

TESTS AND ASSAYS

Scope. The requirements are not framed to take account of all possible impurities. It is not to be presumed, for example, that an impurity that is not detectable by means of the pre-

MODIFICATION OF PHYSICAL PROPERTIES AND DRUG DELIVERY RATES FROM POLYDIMETHYLSILOXANE BY USE OF SELECTED OIL AND WATER SOLUBLE ADDITIVES

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INTRODUCTION

Silicone medical grade elastomers (polydimethylsiloxanes) are biocompatible, non-bioerodable and chemically inert polymers which are ideal for use in controlled drug delivery systems. Polydimethylsiloxane elastomers are employed as rate controlling membranes and matrices for both human and veterinary pharmaceutical implant and transdermal dosage forms.

Until recently, delivery of drugs from "hydrophobic" polydimethylsiloxanes were limited to lipophilic and non-ionic drugs. It has been demonstrated that release of hydrophilic drugs such as melatonin (1), morphine sulfate (2) or sulfanilamide (3,4) can be enhanced from polydimethylsiloxane elastomers which are co-formulated with hydrophilic excipients such as glycerol, polyethylene glycol (PEG 400), sodium chloride, and sodium alginate. It is well recognized that the permeation rate of liphophilic drugs, such as progesterone, is several orders of magnitude greater through silicone elastomers compared to other organic polymers (5). However, there have been few reports on effective methods for modifying the permeation rates of lipophilic drugs from silicone polymeric delivery systems.

The objective of the present study was to: a) evaluate the effects of a wide variety of pharmaceutical excipients, surfactants, and skin penetration enhancers when formulated with Q7-4840 medical grade polydimethylsiloxane liquid silicone rubber (Q7-4840) on cure and resultant physical properties of the elastomer, and b) determine the permeation rate of progesterone through selected excipient modified silicone membranes.

EXPERIMENTAL

1. Cure Compatibility Screen

Initial studies evaluated the compatibility and maximum wt% loading level of 4 classes of pharmaceutical excipients with Q7-4840 (Dow Corning Corp., Midland, MI). Formulations were prepared by blending in a ratio of 1:1 the appropriate quantity of parts A and B of Q7-4840 and each excipient (0, 2, 10, 30, and 50 wt%) to yield 10 grams of each sample. The rate and extent of vulcanization was monitored in a Monsanto Rheometer (Model 100, Monsanto Company, Akron, Ohio) over a period of 60 minutes at 100°C with an arc setting of 3°. An excipient was considered to be compatible with Q7-4840 if greater than 1 lb. in. of torque was generated and the formulation resulted in a dry tack free elastomer.

2. Preparation of Silicone Membranes

Membranes of Q7-4840 containing the maximum wt% loading level of each excipient were prepared for physical property testing and permeation studies. Membranes were prepared by compression molding at 100°C for 15 minutes and post cured in a hot air circulating oven. Membranes employed in permeation studies were die cut into 2.5 inch dia. discs.

3. Evaluation of Physical Properties

The following physical properties of excipients modified Q7-4840 elastomers were evaluated according to ASTM methods: durometer (D2240), tensile strength, elongation, and modulus at 100% (D412). Differential scanning calorimetry was employed to determine glass transition (Tg) and melt temperatures (Tm) of the modified elastomers.

4. Membrane Permeation Studies

Progesterone was selected as a molecular probe for comparing permeation through excipient modified Q7-4840 silicone membranes. Studies were performed in a Ghannam-Chien membrane permeation system (Bellco Biotechnology, Vineland, NJ) at 37°C and 700 RPM. The donor compartment was filled with 170 ml of a supersaturated progesterone solution of 40% PEG 400 (v/v); while the drug free solution was filled into the receptor compartment. Receptor solution was sampled at 30 min. intervals over a 6 hour period during which ideal sink conditions were maintained. Steady state permeation rates, time lag, and apparent diffusivity were determined.

RESULTS AND DISCUSSION

1. Physical Properties of Modified Membranes

Table 1 shows the physical properties of control and excipient modified Q7-4840 modified membranes. In general, fluid additives result in elastomers having lower durometers (i.e. softer) compared to control. In contrast, the water and oil soluble solid excipients resulted in elastomers having higher durometers (i.e. harder) compared to control. Although, in all cases, the excipients reduced the tensile strength, modulus and elongation of the elastomers, they were still considered suitable for fabricating rate controlling membranes. Control elastomers had a low Tg and Tm of -125°C and -63°C, respectively. The excipients did not alter the chemical structure of the polymer since Tg and Tm were not changed.

2. Membrane Permeation Studies

Table 1 and Figure 1 show the enhancement of progesterone permeation produced by silicone membranes containing selected fluid additives, except propylene glycol which decrease permeation. Table 1 shows the reduction in progesterone permeation through silicone membranes containing various solid excipients. The reduction in progesterone permeation rate was proportional to the wt% loading level of Methocel in the Q7-4840 membrane (Figure 2). In general, progesterone permeation rates were

enhanced through membranes containing fluid additives and reduced through membranes containing solid additives. The effects on diffusivity were less predictable. A good correlation (r = -.826) was found between progesterone permeation rate and Shore A durometer (Figure 3).

Table 1

Effect of Excipients on Physical Properties and Progesterone Permeation through Modified Q7-4840 Membranes

EXCIPIENT (WT%)	PROPERTIES[a] DUR	TEN	ELONG	MOD	PER
Control	41	1360	586	168	1.9
Fluid Additives					
Isopropyl palmitate, 30	14	383	475	58	4.9
Light mineral oil, 30	19	252	298	74	3.7
Coconut oil, 10	28	752	455	130	2.8
Azone, 2	12	175	528	45	2.6
20 cs., 360 fluid, 30[b]	18	431	448	61	2.2
Glycerol, 10	39	987	497	145	1.9
Propylene glycol, 10	41	752	344	130	1.7
Solid Additives					
Lactose, 30	53	378	314	117	1.3
d-Sorbitol, 30	47	283	226	126	1.1
Polyvinylpyrrolidone (PVP), 30	62	249	314	98	1.0
Methocel, 30	66	339	223	277	1.0
Sodium lauryl sulfate (SLS), 30	47	229	255	132	0.5
Stearyl alcohol, 10	39	480	358	122	ND[c]

[a] durometer, Shore A (DUR), tensile strength, ppi (TEN), elongation, % (ELONG), modulus 100%, ppi (MOD), permeation rate, ug cm/cm^2 min. x 10^2 (PER). Each value is the mean of triplicate determination.

[b] polydimethylsiloxane fluids (Dow Corning Corp.)

CONCLUSIONS

These results demonstrate the compatibility of a wide variety of pharmaceutical excipients with Q7-4840 silicone elastomer. The resultant physical properties and permeation rates of lipophilic drugs can be modified by co-formulating Q7-4840 polydimethylsiloxane with the appropriate additive and wt% loading level.

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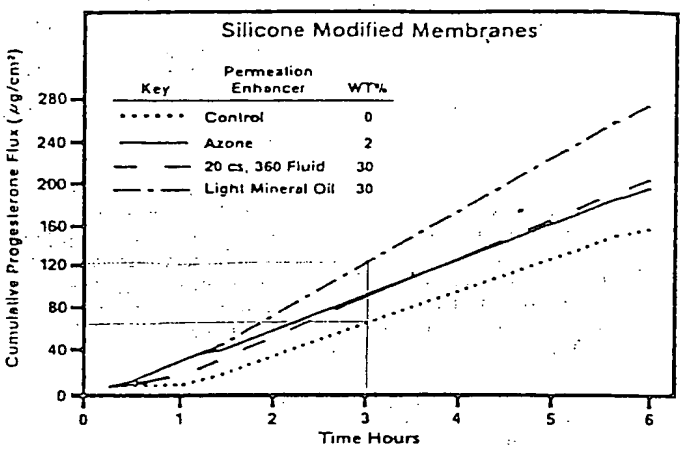

Figure 1: Enhancement of Progesterone Permeation through Fluid Modified Silicone Membranes

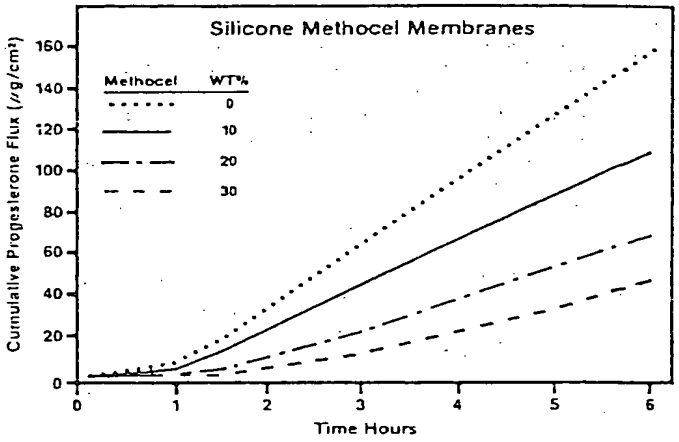

Figure: Reduction of Progesterone Permeation through Silicone Membranes Modified with Methocel

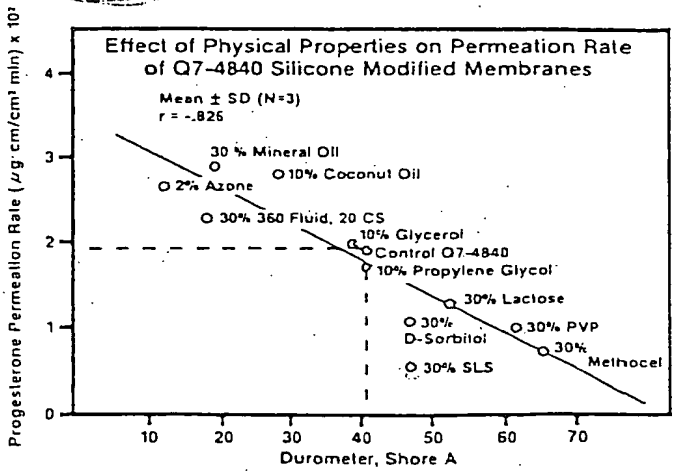

Figure 3: Effect of Durometer, Shore A on Progesterone Permeation through Excipient Modified Silicone Membranes